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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,787	07/21/2003	Congxin Liang	038602-1617	4271

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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 07/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,787	LIANG ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/21/03 & 6/24/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11 and 22-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11 and 22-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/21/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 7/21/03 and the amendments of 6/24/04. There are twenty-four claims pending and twenty-four under consideration. Claims 1-3 and 5-11 are compound claims. Claims 22-24 are composition claims. Claims 25-35 are method of using claims. This is the first action on the merits. The application concerns some Pyrrolo[2,3-b]pyridin-2-one compounds, compositions, and uses thereof.

Title

2. After restriction, the title of the invention is no longer descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following is suggested: replacing "7-AZA-INDOLIN-2-ONES " by " Pyrrolo[2,3-b]pyridin-2-ones".

Priority

3. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. Also, the current status of all nonprovisional parent applications referenced should be included.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 5-10, and 22-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the definitions of R_2, R_3, and Y in claim 1, Applicants employ the open term "comprising". What else may be attached to Formula I?

5. Claims 1-3 5-10, and 22-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the definitions of R_2, R_3, X, and Y in claim 1, Applicants repeatedly employ the phrase "optionally substituted". Substituted by what?

6. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "and derivatives thereof" is indefinite for we do not know which compounds are contemplated. A derivative is the result of a reaction upon an organic molecule. Since we do not know the reagents or the conditions of these reactions, there is no way of determining the

structures of the claimed "derivatives". The phrase "derivatives thereof" is, in essence, a product by process claim. Yet Applicants have not described the intended processes sufficiently that we may understand the structures of the compounds they claim.

7. Claims 22, and 24-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 22, 25, and 32 are independent claims, yet all refer to Formula I whose structure is not given in each claim.

8. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "a mammalian disease characterized by unregulated protein kinas activity". It is unclear what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases

Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

9. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim depends upon claim 30, which is drawn to cell culture, yet claim 33 lists a number of diseases. Was dependency upon claim 32 intended?

10. Claim 34 recites the limitation "cancer" in line 2. There is no antecedent basis for this limitation in the parent claim 31, which does not recite cancer. Cancers generally are not understood to be a protein kinase related diseases. Was dependency upon claim 33 intended?

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-11, and 22-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates, clathrates, or prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one

skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found in paragraph 8, page 20. There is no specific direction concerning solvates or clathrates. c) There is no working example of a solvate, clathrate, or prodrug of a compound the formula I. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body.

e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that

paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. The artisan preparing the solvates and chathrates would be a B.S. chemist with several years experience in scale-up or pilot plant work. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced

into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list potential prodrug derivatives and solvents embraced by claim 1.

Thus, undue experimentation will be required to determine if any particular ester is, in fact, a prodrug.

12. Claims 25-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting EGFR and Gst-Flk1 in cell

culture, does not reasonably provide enablement for treating any claimed disease or inhibiting the other listed enzymes. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered in making an enablement rejection have been summarized above. The two issues concerning diseases and the enzymes will be discussed separately. The three main issues concerning diseases are the lack of any correlation between clinical efficacy for disease treatment and Applicants' *in vitro* enzyme inhibition assays, the state of the prior art, and the breadth of the claims.

There are five assays described in pages 61-79 with data on 48 compounds in the EGFR and Gst-Flk1 assays. Applicants do not state and it is not recognized in the cancer arts this assay is correlated to clinical efficacy for treating diseases. The state of the clinical arts in EGFR enzyme inhibition pharmacology diseases is provided by Bridges (Chem. Rev.). Bridges (Chem. Rev.) states in the Epilog, "[t]here is no guarantee that [CI-1033: a soluble, irreversible inhibitor of EGFr autophosphorylation] will be found efficacious in Phase II/III trials or that the ideal drug cocktails containing it will be identified. Even if the compound works, there

is no guarantee that it will prove to be better in the clinic than its rivals, known or unknown, and finally no guarantee that if it makes it to the market, that it will ever sell well enough to recoup its development costs. If this review had been written by anyone else developing kinase inhibitors, they could easily have ended their story on a similar cautionary note, as no kinase inhibitor is yet on the market, helping patients, and generating revenue." Cohen (J Clin Oncol.) reports in his abstract that ZD1839, an orally active, selective EGFR tyrosine kinase inhibitor, is active in a phase II study of squamous cell carcinoma of the head and neck. Thus, even four years after Applicants effective filing date, the most skilled oncologists have not been able to learn how to use such inhibitors for the treatment of any cancer named in claim 35.

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the hundred of diseases embraced by the terms cancer, metabolic disorders, and nervous system disorders. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.

Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

13. While Applicants describe three additional protein kinase assays, there are no compounds of the present application showing activity in them. Claims 27 lists dozens of additional kinases for which tests are not even described. The nature of the invention requires an understanding of all these diverse enzymes and enzyme binding activity. The enzymes are structurally unrelated and in view of the unpredictability of enzyme binding activity and the diverse substituents on the molecules of formula I, the skilled enzymologist would in deed question reasonably the ability of those compounds to inhibit all the enzymes of claim 27.

Conclusion

14. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

15. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK/me